

Perspectives of Acupuncture Intervention on Bell's palsy in Post COVID-19 infections: A Review

Abstract:

Objectives:

To evaluate the clinical evidence of acupuncture treatment for Bell's palsy in post COVID-19 infection.

Methods:

A comprehensive literature search was conducted by two independent investigators using PubMed, MEDLINE, Google scholar, LILACS and the Cochrane Register of Controlled Trials and others from 2000 up until 2021, using the following keywords: Bell's Palsy, covid-19, acupuncture, Mucormycosis, vaccine and steroids.

Selection of articles was restricted to full-text articles published in English language only. We included all randomized controlled trials (RCTs) that compared the clinical effects of an acupuncture intervention (acupuncture used alone or add on) with no treatment. Accordingly, RCTs fulfilling the criteria were studied.

Results:

Most of the studies were generally of low methodological quality and only six randomized controlled trials (1117 people) were finally included for the study. In all of the included studies the treatment group or the acupuncture group reported advantageous effects or better outcomes compared to baseline or control group. No adverse events were reported in any of the included studies.

Conclusions:

Our review suggest that Acupuncture can be an adjunct or a good alternate therapy for patients with Bell's palsy post recovery of COVID-19 infection and especially those with the risk of predisposed factor for mucormycosis and other severe health complication. However, the present evidence might not be sufficiently robust against methodological flaws of the included RCTs. Well-designed trials and high methodological qualities are essential to establish a strong conclusion about the efficacy of acupuncture for Bell's palsy.

Keywords: Bell's Palsy, covid-19, acupuncture, Mucormycosis, vaccine, steroids.

1.Introduction:

Bell's palsy is an acute peripheral lower motor neuron [LMN] facial nerve palsy, characterised by weakness on one side of the face, unilateral, partial, or complete paralysis of the face without any

other neurologic abnormalities on examination(1,2). Named after Sir Charles Bell, a Scottish anatomist, it is the most common acute mono-neuropathy affecting a single nerve, and also the most common diagnosis associated with facial nerve weakness and paralysis(3). Bell's palsy is a common cranial neuropathy with a rapid unilateral facial nerve paresis [weakness] or paralysis leading to the partial or complete inability to voluntarily move facial muscles on the affected side(4). It usually occurs in a lower motor neuron associated with partial or complete weakness, numbness, increased sensitivity to sound, mild pain and altered taste(2). The facial paresis or paralysis that occurs in Bell's palsy may also cause temporary oral incompetence and difficulty in closing the eyelid, leading to potential eye injury(3). Usually, most of the people affected with the condition make a spontaneous recovery within 1 month, but up to 30% show delayed or incomplete recovery(2). Poor outcomes for prolonged period do occur and can be devastating to the patient. The cause of Bell's palsy is often unknown or largely remains idiopathic however, re-activation of herpes virus at the geniculate ganglion of the facial nerve by herpes simplex virus isoform 1 [HSV 1] and herpes zoster virus [HZV] are thought to be the most likely causative factor(1,2,4,5). Although the exact cause and mechanism remains unclear, other potential contributors to the development of Bell's palsy may include Immune, infective and ischaemic mechanisms(4). A cell-mediated autoimmune mechanism could also play a potential role in pathogenesis of Bell's palsy(5). Bell's palsy is most common in people aged between 15 to 40 years affecting both male and female population equally, although the incidence may be slightly higher in pregnant women(2,5). The targeted treatments are generally designed to improve facial function and facilitate recovery. There are multiple treatment options for Bell's palsy, although some still remains controversial for their effectiveness or efficacy(3). The overall treatment may include oral steroids, oral antiviral therapy and other multidisciplinary system such as physical therapy and acupuncture.

COVID-19 and its association with Bell's palsy

Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], the novel virus that causes coronavirus disease 2019 [COVID-19] was first identified in Wuhan, a city in Hubei province of China, in December 2019 (6,7). The clinical manifestations of COVID19 are now known to involve multi-systemic involvement in the body and not just confined to pulmonary or cardiac pathology. The cytopathic effect of the virus on different organ system have been studied through histopathological analysis of biopsies revealing vast involvement of virus on multiorgan system(7). Fever, cough and dyspnoea are the commonest symptoms of COVID-19 disease, however, non-respiratory presentations which include neurological manifestations have been increasingly recognized(8). At present, evidences are now growing for the increasing neurological symptoms around the world (1,9). Both central and peripheral nervous systems can be affected in COVID-19(10). Among many other neurological complications, there have been reported cases of associated cerebrovascular accidents with large vessel occlusions, posterior reversible encephalopathy syndrome, cerebral venous sinus thrombosis, acute necrotizing encephalopathy, meningoencephalitis, epilepsy, ophthalmoparesis, myasthenia gravis, hyposmia, hypogeusia, Guillain-Barré syndrome, and motor peripheral neuropathy etc.(9–12).

Various studies have also reported incidence of the facial nerve palsy during the COVID-19 pandemic with most studies reporting facial palsy as one of the first presenting symptom or occurring within the first week of onset COVID-19 or testing positive to COVID-19 test. The symptom can be seen at any time during the course of COVID-19 infection and can sometimes manifest as late as one month after the diagnosis(1). It has also been reported after vaccination(13–15). The first case of severe acute respiratory syndrome coronavirus 2- induced facial nerve palsy assessed by 18fluoro-2-deoxy-d-glucose [18FDG] positron emission tomography-computed tomography [PET/CT] was reported in a study(8). Another study also highlights the case series of eight patients with peripheral facial palsy during COVID-19 infection seen from May to July 2020 in which, facial palsy was the first symptom

observed in three patients(16). In a prospective cross-sectional study, forty-one patients were included for the study of which 21 patients had left-sided and 20 had right-sided paralysis, indicating facial paralysis to be the only symptom of COVID-19(17).

In another study, of the total 34 patients, 8 of them tested positive to RT-PCR to COVID-19. Among the 8 patients who tested positive, 5 of them showed peripheral facial paralysis one of the manifestations of COVID-19, which suggests that peripheral facial palsy could be a sole symptom in COVID-19(18). The progressive and gradual onset on development of right sided deviation of mouth with incomplete closure of the left eye over a period of three days was also reported in a case report indicating Bell's palsy could be a possible neurological complication of COVID 19 infection(19). Incidences of bell's palsy during COVID -19 has also been reported in cases of pregnancy, post-natal and paediatric involvements which signifies the potential neurological threat of Covid-19 disease. A 35-year-old woman, primigravida, 39-week gestation, diagnosed with COVID-19 after presenting with isolated peripheral facial palsy was reported in a case study(20)[20]. Similarly, lower motor neuron facial palsy of the right facial nerve associated with COVID-19 in a post-natal mother has also been reported in a case presentation. Several other cases of covid-19 associated bell's palsy during pregnancy has also been reported around the world(21). A prospective study in the United Kingdom conducted over a 19-weeks, from 14 February to 24 June 2020 demonstrated a significant increase in the incidence of paediatric Bell's palsy during the peak of the Covid-19 infection(22).

Pathophysiological manifestation

There are many other reports that have been published across various journals for bell's palsy and covid 19 related infections although, the exact mechanisms and interrelation between the two diseases mostly remains idiopathic or scarce till date. However, there are several understandings and hypothesis that have been developed according to the clinical presentations and findings. Generally, SARS-CoV-2 virus enters the brain either via a hematogenous route of olfactory system. A possible viral entry point could be Angiotensin-converting enzyme two receptors [ACE 2] present on endothelial cells of cerebral vessels(10). The penetration of the virus to the central nervous system results into a myriad of CNS complications due to intracranial storm(9). Decreased metabolic activity in the facial nerve of the affected side compared with the contra-lateral side may suggest a reduced blood flow to the nerve secondary to micro thrombosis in the perineural arteriovenous plexus—a common phenomenon due to SARS-CoV-2-induced endothelial injury in the pulmonary and several other microvascular beds(6). In addition to vascular injury, the binding of coronavirus to angiotensin-converting enzyme 2 [ACE2] receptors, which are widely distributed on glial cells and neurons through neurotrophic effects of SARS-CoV-2 could infect the neurons or supportive non-neural cells such as glia(1,6). These may lead to nerve damage through direct injury, autoimmunity, and inflammatory demyelination or ischemia of the vasa nervorum(1).

Conventional Treatment Interventions in Bell's palsy

As per the clinical practice guidelines on Bell's palsy, the first line or recommended treatment includes administration of oral-steroids and anti-viral therapies. Prescription of oral steroids within 72 hours of symptom onset in 16 years and older for Bell's palsy patients has been recommended. Steroid monotherapy is usually recommended for acute treatment of Bell's palsy as the use of combined therapy still remains controversial for severe cases. Clinicians may also prescribe a combination of oral steroid and oral anti-viral therapy within 72 hours of symptom onset for patients with Bell's palsy(3,4). Commonly used drugs for the management of Bell's palsy include oral corticosteroids such as prednisolone and antiviral drugs like acyclovir and valaciclovir. Eye drops, such as Hypromellose drops should be applied for lubrication and protection of eye to prevent long-

term complications(3,23). Surgical decompression is usually not recommended in most cases and are rarely done in rare cases in order to assess the incomplete return of facial motor function and synkinesis in some patients with Bell's palsy(3,23,24).

Table 1: Summary of 6 RCTs included in the study;

Refs/Studies	Intervention method	Assessment types	Acupuncture sessions	outcomes
<i>A multicentral randomized control study on clinical acupuncture treatment of Bell's palsy.</i>	Manipulative acupuncture (twirling, lifting, and Thrusting) plus moxibustion	Symptoms and sign assessment, House–Brackmann grading scale (HBGS) and facial disability indexes (FDI).	5 sessions per week for 4 weeks. Duration 30 mins	Two treatment group showed better result than that of control group in cure plus marked relief rates(P<0.05), cure rate (P<0.05), HB Scale(P<0.01), FDIP scores(P<0.01).
<i>Effectiveness of strengthened stimulation during acupuncture for the treatment of Bell palsy: A randomized controlled trial.</i>	Manipulative acupuncture (twirling, lifting, and Thrusting) with <i>de qi</i>	House–Brackmann Scale, the Facial Disability Index and Quality of Life scale	5 sessions per week for 4 weeks. Duration 30 mins	Assessment of FDI, HB Scale and QOL shows better result in <i>de qi</i> group than that of control group. <i>De qi</i> score was higher in <i>de qi</i> group than in control group-(p<0.001)
<i>Effect of acupuncture combined with blood-letting by a three-edged needle on 50 cases of Bell's palsy at the acute stage.</i>	Manipulative acupuncture (twirling, lifting, and Thrusting) plus three-edge needle (bloodletting)	Symptoms and sign assessment, House Brackmann Grading System	5 sessions per week for 4 weeks. Duration 30 mins	Symptoms and sign assessment score and therapeutic effect in treatment group was better in treatment group(p<0.05)
<i>Efficacy of Manipulative Acupuncture Therapy</i>	Manipulative acupuncture (twirling, lifting, and Thrusting)	facial nerve functioning was scored (HBGS) and clinical	3 sessions per week for 8 weeks. Duration 30 mins	Recovery rate in manipulative acupuncture (53.3%) was

<i>Monitored by LSCI Technology in Patients with Severe Bell's Palsy: A Randomized Controlled Trial.</i>	assisted by LSCI	efficacy		higher than simple acupuncture (33.9%) after 8 weeks (P<0.05) and at 6 months (91.7% vs. 78.0%; P < 0.05).
<i>The Efficacy of Acupuncture in the Treatment of Bell's Palsy Sequelae.</i>	electroacupuncture and Nogier ear acupuncture	the facial nerve compound motor action potential, HouseeBrackmann (HB) and Sunnybrook (SB) grading scales	3 sessions per week for 4 weeks. Duration 30 mins	Pre- and post-treatment CMAP values within acupuncture group (p= 0.036). SB and HB showed significant difference in pre and post treatment. improvement rate higher in acupuncture group than that in control group
<i>Acupuncture for the sequelae of Bell's palsy: A randomized controlled trial.</i>	Manipulative acupuncture (twirling, lifting, and Thrusting) with <i>de qi</i>	Facial Disability Index (FDI) social and well-being subscale, FDI physical function subscale, the House–Brackmann score, the Sunnybrook Facial Nerve Grading system, lip mobility and stiffness	3 sessions per week for 8 weeks. Duration 10 mins	At 8th weeks, acupuncture group had greater improvements in the FDI social and physical score, Sunnybrook Facial Nerve Grading score and stiffness index

2.Methods:

A comprehensive literature search was conducted by two independent investigators using PubMed, MEDLINE, Google scholar, LILACS and the Cochrane Register of Controlled Trials and others from up 2000 until 2021.

Inclusion criteria:

Selection of articles was restricted to full-text articles published in English language only. All randomized controlled trials (RCTs) that compared the clinical effects of an acupuncture intervention (simple acupuncture or electro-acupuncture combined with moxibustion, three-edge needle and Nogier ear acupuncture) with no treatments were included in our study.

Exclusion criteria:

Whereas studies published in language other than English, non- RCTs, Sham acupuncture, Gray literature such as conference abstracts and unpublished reports were excluded from the study.

Using these parameters, we identified 309 published articles. From those, only 6 RCT's involving 1076 subjects matched the inclusion criteria and were reviewed.

3.RESULT:

Summary of search result:

The included RCTs studied both male and female population across studies. The sample sizes ranged from 39 to 439 subjects with a total of 1076 subjects whereas an average acupuncture treatment duration lasted for 30 minutes spanning across 4 to 8 weeks. Across studies, acupuncture methods used were mostly manual acupuncture (with manipulations) however some studies used acupuncture along with moxibustion, bloodletting and electroacupuncture as intervention. Of the total 6 RCTs 4 studies were done across China, one each in turkey and South Korea respectively. The Summary of 6 RCTs included in the study are enlisted in the table 1

Acupuncture vs Acupuncture Combined with basic treatment vs Basic treatment

To establish the therapeutic effects of acupuncture and moxibustion on Bell's palsy a study was done across four hospitals involving 439 cases in a multicentral Randomized control Study. In this study the patients were randomly divided into 3 groups **vis** first treatment group (acu-moxibustion group - treated with filiform needle and moxibustion), and second treatment group (basic treatment like in control group along with acu-moxibustion like in acu-moxibustion group) and a control group (basic treatment group -treated with prednisone, vitamin B12, vitamin B1, and dibazol). The study observed that the therapeutic effects two treatment group showed better result than that of control group in cure plus marked relief rates($P<0.05$), cure rate ($P<0.05$), HB Scale($P<0.01$), FDIP scores($P<0.01$). Thus, Acupuncture and moxibustion treatment may exert better therapeutic effects on Bell's palsy as compared to the basic treatment alone or the basic treatment combined with acu-moxibustion.(25)

Acupuncture with stimulation (*de qi*) Vs Acupuncture without stimulation (*de qi*)

Another multicentre randomized controlled trial involving 338 patients with Bell palsy was carried out at 11 tertiary care hospitals in China. In the study, patients were randomly assigned to the control group ($n = 171$) or *de qi* group ($n = 167$) with both groups receiving Acupuncture intervention. In the *de qi* group, manual needle manipulations were done until *de qi* was reached, however the needles were inserted without any manipulation in the control group. The *de qi* was assessed during the 1st, 5th, 10th, 15th and 20th sessions, immediately after removing the needles from the patients. After 6 months, assessment of Facial disability index, House–Brackmann score and Quality of life shows better result in *de qi* group than that of control group. The *de qi* score was higher in *de qi* group than in control group- $(p<0.001)$. The study observed that acupuncture stimulation that elicited *de qi* had a better therapeutic effect as compared to acupuncture without stimulation among patients with Bell palsy(26)

Simple Acupuncture Vs Acupuncture plus blood-letting

In the third RCT, 100 patients were randomly divided into a control group (50 cases) treated by simple acupuncture and a treatment group (50 cases) treated by acupuncture plus blood-letting using three-edged needles for Bell's palsy. Both groups received acupuncture once a day with 30 minutes of needle retention for 5 days consecutively, as the first course of treatment which was followed by 3 more courses of treatments. In the first course of treatment for 5 consecutive days, bloodletting method was used with 8–10 drops at bilateral Guanchong (TE 1) and the apex of ear along with acupuncture in the treatment group. A significant improvement in the scores for symptoms and signs were observed after the treatment in both groups ($P < 0.05$ or $P < 0.01$) however after a month, the treatment group showed better improvement as compared to the control group with a significant difference ($P < 0.05$)(27).

Acupuncture with manipulation Vs Acupuncture without manipulation

The fourth RCT included 120 newly diagnosed patients with severe Bell's palsy where one group received manipulative acupuncture (twirling, lifting, and thrusting) and the other group were treated with simple acupuncture (without manipulation- twirling, lifting, and thrusting). Both groups received a total of 24 sessions with a frequency of three times per week lasting 30 min for each treatment. Following 8-week treatment, a significant improvement was seen in both groups however, manipulative acupuncture group showed a better recovery rate (53.3%) as compared to simple acupuncture group (33.9%) with $P < 0.05$). Six months after the initial onset of facial palsy, follow up studies also revealed a significantly higher recovery rate (91.7% vs. 78.0%; $P < 0.05$) indicating that manipulative acupuncture therapy could be a better treatment option for severe Bell's palsy as compared with simple acupuncture therapy(28).

Acupuncture Vs Without Acupuncture Treatment

In our fifth RCT, a total of forty patients with Bell's palsy sequelae were randomly divided to either the acupuncture or the control group (no-acupuncture waiting list). The acupuncture group received electroacupuncture and Nogier ear acupuncture intervention three times per week for 4 weeks (12 sessions), whereas control group received no acupuncture during the entire session. The facial nerve compound motor action potential, HouseeBrackmann (HB) and Sunnybrook (SB) grading scales were used to assess the pre and post treatment clinical outcomes. A significant difference within the two groups were observed following the pre-treatment and posttreatment analysis where significant level of improvement rate was seen in acupuncture group as compared to that of no acupuncture group (control group). The study, found that acupuncture treatment can be a safe and effective method in the treatment of Bell's palsy sequelae(29).

In another study with Bell's palsy sequelae 39 subjects were randomly divided into two groups, an acupuncture group ($n = 26$) and a control group ($n = 13$). Post randomization, acupuncture group received a total of 24 acupuncture sessions with a frequency of three times per week over a period of 8 weeks. However, the control group did not receive acupuncture intervention during the entire 8-week period. The acupuncture group as compared with the control or waiting list group showed greater improvements in the Facial Disability Index (FDI) social score, FDI physical function subscale, Sunnybrook Facial Nerve Grading score and stiffness scale. The study indicates that acupuncture may exhibit better therapeutic effects on the social and physical aspects of Bell's palsy sequelae(30). The summary of the most commonly used acupuncture points across the study are listed in the table 2.

Table 2: Commonly and frequently used acupuncture points:

Acupuncture point	Frequency of appearance in RCT's
ST4 (Dicang)	6
LI4 (Hegu)	6
ST6 (Jiache)	5
GB14 (Yangbai)	5
TE17 (Yifeng)	5
ST7 (Xiaguan)	3
LI20 (Yingxiang)	3
ST36 (Zusanli)	2
LI10 ((Shou San Li)	2
BL2 (Zanzhu)	2
TE23 (Sizhukong)	2
ST2 (Sibai)	2
SI18 (Quanliao)	2
EX HN5 (Taiyang)	2

4. Discussion:

In Bell's palsy, acupuncture treatment is thought to regulate channels and collaterals, harmonize Qi and blood circulation, strengthen the body's resistance, increase nerve excitability, promote nerve regeneration and formation of its collateral branches, enhance muscle contraction and blood circulation, improves metabolic and body functions. Oral steroids and oral anti-viral drugs have been widely used for treating Bell's palsy and other related facial palsies till date. However, there is a need to ponder upon the use of steroids used, especially after severely affected COVID-19 infection due to an alarming raise in the number of mucormycosis cases around the world(31). The oral steroids commonly used for treating Bell's palsy despite showing effective results, possess wide array of adverse drug reaction and should be used with caution in immunocompromised patients. Acupuncture, a part of traditional Chinese medicine (TCM), involves inserting fine needles into specific points on the skin or applying various other techniques to the acupuncture points in the body to bring about healing.

Role of Acupuncture in alleviating endothelial injury

The basic mechanism related to the idiopathic facial nerve injury includes ischemia of vasa nervorum and inflammation of the nerves. Some of the recent studies have shown the hypercoagulability state resulting in vascular endothelial damage in some COVID-19 infected patients with Bell's Palsy. These microthrombi and other vascular endothelial changes which have been consistently reported in several post-mortem studies may be directly or indirectly implicated in the development of facial nerve ischemia in COVID-19 patients. The endothelial injury around the pulmonary and microvascular beds reduces the arterial supply to the perineural arteriovenous plexus leading to decreased metabolic activities of the facial nerve(32).

Acupuncture or electroacupuncture has been found to have a significant effect on the various endothelial injury and nerve damage. Some studies suggests that it could regulates cerebral blood flow as well as exerts anti-apoptosis effect in the ischemic area meanwhile promoting neurogenesis and cell proliferation in the central nervous system (CNS) besides regulating the neurochemicals(33).

Studies suggest that specific acupuncture points such as ST36 (Zusanli), LI 11 (Quchi), GV14 (Dazhui) and LI4 (Hegu) can improve cognitive hippocampus function, inhibits oxidative damage, improves the expression of different anti-inflammatory mediators, promotes neuronal cell proliferation, improves perfusion at the ischemic zone, angiogenesis and exhibits anti-apoptotic effect. Acupuncture can improve endothelial dysfunction and promotes blood flow by decreasing the vascular resistance through the expression of endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS). It has been reported that production of Nitric oxide was enhanced by electro-acupuncture (EA) on Zusanli (ST36). This could promote the blood flow to the affected area around the perineural arteriovenous plexus of the facial nerves(34).

Role of Acupuncture in Inflammation of Nerve

Inflammation of facial nerve is one of the common pathological factors in facial nerve palsy. The action of SARS COV2 binding with ACE 2 receptors (viral interaction) in the Neurons and the Glial cells in particular could lead to nerve damage through direct viral action, autoimmunity, inflammatory demyelination and ischemia of Vas nervorum. Glial cells (astrocytes, oligodendrocytes and microglia) interact with different neurons, immune cells, blood vessels and act as the first line of defence mechanism against nervous system stimulation. The microglial cells belonging to the monocyte and macrophage lineage forms the innate immune system and are the most active immune cells in the CNS. (35)They are responsible for the initial response and immune signalling to the astrocytes, eventually leading to neuroinflammation which is a complex innate immune response process during pathological manifestations of central nervous system (CNS) injury. Various studies have shown that manual acupuncture or electroacupuncture can effectively inhibit glial cell activation, excessive proliferation, and structural damage to astrocytes after CNS injury. Specific acupuncture points such as GV6, GV9, GV20, GV29, ST36, LI4 and LI11 can particularly inhibit or down-regulate the pro-inflammatory and inflammatory factors such as TNF-alpha, IL-1Beta, IL-6 etc. GV 20, and ST 36 can improve microglial degeneration, cognitive hippocampus function, stimulates neurogenesis and exerts a neuroprotective role against oxidative damage as well as down-regulate TNF-alpha, IL-1Beta, IL-6, thereby preventing apoptosis and necrosis of neurons. GV20, BL60 and LI4 with electroacupuncture can also inhibit the NF-KB signalling pathways thereby disrupting the interaction of various chemokines and their receptors around the ischemic injury(36).

In addition to this most of the Peripheral nerve injury not only affects the site of the injury, but can also induce neuronal apoptosis at the spinal cord. In this regard focusing only at the site of injury by selecting acupuncture points entirely along the injured nerve trunk and neglecting other specific acupuncture points may delay the onset of treatment efficacy and rehabilitation as a whole. An effective acupuncture treatment may include a multiple acupuncture point stimulation rather than a single point stimulation. Keeping in mind the significance of few acupuncture points studied, combination of acupuncture points from various meridians such as the commonly used points ST4, ST6 along with ST36, LI4 and LI 11, GV9 and GV20, BL2, BL60 with de qi stimulation could be incorporated for better efficacy of the treatment(37).

5. Conclusion

There is significant evidence available broadly in favour of acupuncture for the treatment of Bell's palsy that can be used as an adjunct or alternative, however more rigorous clinical trials and studies are required to establish the role of acupuncture in the management of Bell's palsy. Clinical trials with significant numbers of subjects, well-designed, clearly reported randomised controlled studies can further boost the efficacy and effectiveness of acupuncture in the management of Bell's palsy and related disorders. Furthermore, additional studies should also examine the possibility of combination

therapies with other standard therapeutic interventions or adjuvants to develop a safer and more effective way to treat Bell's palsy.

Abbreviations:

RT-PCR: Reverse transcription-polymerase chain reaction

Ethics Statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article.

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Identification

Screening

Eligibility

Included

Fig 1: Flow chart of the literature review.

